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ORIGINAL ARTICLE

Patient-reported outcomes with trastuzumab deruxtecan in hormone receptor-positive, HER2-low or HER2-ultralow metastatic breast cancer: results from the randomized DESTINY-Breast06 trial

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Background: The randomized phase III DESTINY-Breast06 trial (NCT04494425) demonstrated superior efficacy with trastuzumab deruxtecan (T-DXd) versus chemotherapy treatment of physician's choice (TPC) and no new safety signals in patients with hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-low [immunohistochemistry (IHC) 1+, IHC 2+/*in situ* hybridization-negative], and HER2-ultralow (IHC 0 with membrane staining) metastatic breast cancer (mBC). Here, we report the patient-reported outcome (PRO) endpoints in the intent-to-treat (ITT; HER2-low/-ultralow) and HER2-low populations.

Patients and methods: Patients with progressive disease (PD) after one or more prior lines of endocrine-based therapy and no prior chemotherapy for mBC were assigned 1 : 1 to T-DXd 5.4 mg/kg once every 3 weeks ($n = 436$) or TPC [$n = 430$; 59.8% capecitabine; 24.4% nab-paclitaxel; and 15.8% paclitaxel]. PRO questionnaires included the European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30) and breast cancer-specific module (EORTC QLQ-BR45). Changes from baseline (CFB; earliest of 31 weeks or on-study PD) and time to deterioration were assessed.

Results: The median treatment duration was 11.0 (T-DXd) versus 5.6 (TPC) months. In the ITT, the mean CFB scores were similar across treatments in EORTC QLQ-C30 global health status/quality of life (QOL) and functioning scales. T-DXd was associated with less pain [adjusted mean difference −7.2, 95% confidence interval (CI) −9.9 to −4.5] and fewer skin/mucosal symptoms (adjusted mean difference −9.5, 95% CI −11.5 to −7.5), but more nausea/vomiting (adjusted mean difference 7.2, 95% CI 5.3-9.2), appetite loss (adjusted mean difference 6.8, 95% CI 3.6-10.0), and constipation (adjusted mean difference 5.5, 95% CI 2.6-8.4) versus TPC. T-DXd reduced the risk of clinically meaningful deterioration in physical/role/emotional functioning, pain, and fatigue versus TPC, but increased the risk of deterioration in gastrointestinal symptoms. Results were similar in the HER2-low population.

Conclusions: T-DXd preserved QOL while delaying deterioration in physical/role/emotional functioning, pain, and fatigue versus TPC, albeit with more gastrointestinal symptoms. PRO data complement the efficacy/safety of T-DXd in this population.

Key words: metastatic breast cancer, quality of life, trastuzumab deruxtecan, HER2-low, patient-reported outcomes

INTRODUCTION

Patient-reported outcomes (PROs) are increasingly important in evaluating the efficacy and tolerability of clinical trial treatments as part of the overall benefit−risk evaluation.[1] For oncology clinical trials, the US Food and Drug Administration (FDA) advises that the following core PROs should be analyzed:

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disease-related symptoms, treatment side-effects, overall treatment tolerability, physical function, and role function.[2]

Evaluating PROs is important in metastatic breast cancer (mBC) trials as health-related quality of life (HRQOL) can be adversely affected by both the disease and side-effects of treatment, with patients commonly experiencing pain, nausea, and fatigue symptoms.[3] As endocrine therapy (ET) is relatively well tolerated by patients with hormone receptor-positive (HR+) mBC,[3,4] preservation of overall HRQOL and favorable tolerability should be key considerations for additional treatment options in this setting.

Trastuzumab deruxtecan (T-DXd) is an antibody–drug conjugate approved globally for the treatment of patients with unresectable/metastatic human epidermal growth factor receptor 2 (HER2)-low [immunohistochemistry (IHC) 1+ or 2+/*in situ* hybridization-negative (ISH−)] breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during/within 6 months of completing adjuvant chemotherapy, based on results from DESTINY-Breast04 (NCT03734029).[5-7] In the HR+, HER2-low cohort of DESTINY-Breast04, T-DXd improved progression-free survival (PFS) (hazard ratio 0.51, $P < 0.001$; median 10.1 versus 5.4 months) and overall survival (hazard ratio 0.64, $P = 0.003$; median 23.9 versus 17.5 months) versus chemotherapy treatment of physician's choice (TPC).[5] In the same cohort, T-DXd maintained HRQOL despite a longer duration of treatment and the delayed time to definitive deterioration across most prespecified PRO measures of interest, including global health status/QOL (GHS/QOL), physical functioning, and pain versus TPC (51.1% of patients assigned to eribulin, 20.1% capecitabine, 10.3% nab-paclitaxel, 10.3% gemcitabine, and 8.2% paclitaxel).[5,8] As capecitabine is a common first-line chemotherapy in this patient population,[9] an additional PRO analysis of T-DXd versus capecitabine was conducted: both treatments maintained GHS/QOL, but T-DXd also delayed the progression of pain symptoms [hazard ratio 0.42, 95% confidence interval (CI) 0.23-0.78].[10]

DESTINY-Breast06 investigated T-DXd versus TPC in patients with HR+, HER2-low, or HER2-ultralow (IHC 0 with membrane staining) mBC who received one or more lines of endocrine-based therapy and no prior chemotherapy for mBC. At primary analysis (data cut-off: 18 March 2024), T-DXd significantly improved PFS versus TPC in HER2-low mBC (hazard ratio 0.62, $P < 0.001$; median 13.2 versus 8.1 months).[11] Results were consistent in the intent-to-treat (ITT; HER2-low and HER2-ultralow) population (hazard ratio 0.64, $P < 0.001$; median 13.2 versus 8.1 months) and exploratory HER2-ultralow population (hazard ratio 0.78; median 13.2 versus 8.3 months).[11] Safety results were in line with the known profiles of T-DXd and TPC, with no new signals identified.[11] The most common drug-related treatment-emergent adverse events (AEs) were nausea (65.9%) and fatigue (46.8%) with T-DXd (versus 23.5% and 34.3% in the TPC group, respectively).[11]

Aligning with FDA guidance,[2] disease symptoms, treatment side-effects, overall treatment tolerability, and physical/role functioning were evaluated as part of DESTINY-Breast06. Herein, we report the prospectively defined secondary and exploratory PRO study endpoints.

PATIENTS AND METHODS

Trial design

DESTINY-Breast06 (NCT04494425) is an open-label, randomized phase III trial investigating the efficacy and safety of T-DXd versus TPC in patients with HR+, HER2-low, or HER2-ultralow mBC. Patients were eligible if they received at least two prior lines of ET for mBC, or one prior line if they demonstrated disease recurrence within 24 months of starting adjuvant ET or disease progression within 6 months of starting first-line ET plus cyclin-dependent kinase 4/6 inhibitor for mBC. Eligible patients must not have had prior chemotherapy for mBC. Patients were randomly assigned with the use of interactive response technology in a 1 : 1 ratio to receive T-DXd (5.4 mg/kg intravenously once every 3 weeks) or TPC (paclitaxel, nab-paclitaxel, or capecitabine) until disease progression. The ITT population comprised all randomized patients (those with either HER2-low or HER2-ultralow tumor status). Full methods and the trial protocol have been published previously.[11]

Trial oversight

This trial was sponsored by AstraZeneca and Daiichi Sankyo and designed by AstraZeneca in collaboration with Daiichi Sankyo and the study steering committee co-chairs. It was approved by the institutional review board or ethics committee at each investigational site and conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines, the Declaration of Helsinki, and local regulations on the conduct of clinical research. All patients provided written informed consent.

PRO endpoints

PROs were included as secondary and exploratory endpoints in DESTINY-Breast06. The secondary PRO endpoints were analyses of the oncology-specific European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30; v3.0)[12] and the breast cancer-specific module (EORTC QLQ-BR45).[13] The EORTC QLQ-C30 includes GHS/QOL, functioning (physical, role, emotional, social, and cognitive), and symptom scales/items (fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, and diarrhea). The EORTC QLQ-BR45 includes functioning (body image, future perspective, sexual functioning, sexual enjoyment, and breast satisfaction) and symptom scales/items (arm symptoms, breast symptoms, systemic therapy side-effects, upset by hair loss, ET symptoms, skin mucosis symptoms, and endocrine sexual symptoms). The exploratory PRO endpoints included assessment of health status using the EQ-5D 5-level (EQ-5D-5L), patient-perceived

Table 1. Demographics and baseline clinical characteristics of the ITT and HER2-low populations

	ITT[a]		HER2-low[a]	
	T-DXd ($n = 436$)	TPC ($n = 430$)	T-DXd ($n = 359$)	TPC ($n = 354$)
Age (years), median (range)	58.0 (28-87)	57.0 (32-83)	58.0 (28-87)	57.0 (32-83)
Female, *n* (%)	436 (100)	429 (99.8)	359 (100)	353 (99.7)
Race, *n* (%)				
White	231 (53.0)	230 (53.5)	194 (54.0)	186 (52.5)
Black or African American	4 (0.9)	3 (0.7)	1 (0.3)	3 (0.8)
Asian	154 (35.3)	151 (35.1)	122 (34.0)	127 (35.9)
Other	8 (1.8)	12 (2.8)	7 (1.9)	10 (2.8)
Not reported	39 (8.9)	34 (7.9)	35 (9.7)	28 (7.9)
ECOG PS at baseline, *n* (%)[b]				
0	252 (57.8)	257 (59.8)	207 (57.7)	218 (61.6)
1	178 (40.8)	163 (37.9)	148 (41.2)	128 (36.2)
2	1 (0.2)	1 (0.2)	1 (0.3)	0 (0)
HER2 status, *n* (%)				
IHC 0	1 (0.2)	1 (0.2)	1 (0.3)	1 (0.3)
IHC 0 with membrane staining (HER2-ultralow)	76 (17.4)	76 (17.7)	—	—
IHC 1+ (HER2-low)	239 (54.8)	324 (54.4)	238 (66.3)	234 (66.1)
IHC 2+/ISH− (HER2-low)	117 (26.8)	118 (27.4)	117 (32.6)	118 (33.3)
IHC 2+	3 (0.7)	1 (0.2)	3 (0.8)	1 (0.3)
Primary endocrine resistance, *n* (%)[c]	128 (29.4)	140 (32.6)	105 (29.2)	116 (32.8)
De novo disease, *n* (%)	133 (30.5)	132 (30.7)	111 (30.9)	104 (29.4)
Bone-only disease at baseline, *n* (%)	13 (3.0)	13 (3.0)	11 (3.1)	10 (2.8)
Visceral disease at baseline, *n* (%)	376 (86.2)	364 (84.7)	309 (86.1)	299 (84.5)
Liver metastases at baseline, *n* (%)	296 (67.9)	283 (65.8)	243 (67.7)	232 (65.5)
Brain/CNS metastases at baseline, *n* (%)[d]	37 (8.5)	33 (7.7)	33 (9.2)	25 (7.1)
Number of sites of disease, median (range)	3 (1-10)	3 (1-11)	3 (1-10)	3 (1-11)
Lines of ET for metastatic disease				
Number of lines, median (range)	2 (1-4)	2 (1-5)	2 (1-4)	2 (1-5)
Lines of ET, *n* (%)				
1	65 (14.9)	82 (19.2)	54 (15.1)	67 (19.0)
≤6 months on first-line ET with CDK4/6i	37 (8.5)	40 (9.3)	33 (9.2)	33 (9.4)
2	295 (67.8)	288 (67.3)	242 (67.6)	236 (67.0)
≥3	75 (17.2)	58 (13.6)	62 (17.3)	49 (13.9)
Prior therapies for metastatic disease, *n* (%)				
ET monotherapy	230 (52.8)	223 (51.9)	189 (52.6)	183 (51.7)
Any ET based[e]	435 (99.8)	428 (99.5)	358 (99.7)	352 (99.4)
ET with CDK4/6i	388 (89.0)	385 (89.5)	318 (88.6)	316 (89.3)
ET with targeted therapy other than CDK4/6i[f]	143 (32.8)	127 (29.5)	120 (33.4)	105 (29.7)

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Owing to rounding, some percentages may not add up to 100% (see also footnotes).

CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IRT, interactive response technology; ISH−, *in situ* hybridization-negative; ITT, intent-to-treat; mTOR, mammalian target of rapamycin; PARP, poly (ADP-ribose) polymerase; PI3K, phosphoinositide 3-kinase; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice.

[a]HER2-low status determined per IRT data, and HER2-ultralow status determined per central laboratory data; with mis-stratification, the combined sample size of these two populations did not match the ITT total. Two patients were randomly assigned in error to the ITT population (one per treatment group) and were subsequently found to have HER2 IHC 0 without membrane staining per central laboratory testing. One patient who was initially listed as having HER2-ultralow expression per IRT was reclassified as HER2-low based on an updated biopsy (the screening sample was from the premetastatic setting). Therefore, this patient was not included in the HER2-ultralow subgroup analysis or the HER2-low primary population but was included in the ITT population.

[b]A total of 14 patients in the ITT population had missing ECOG PS at baseline ($n = 5$, T-DXd; $n = 9$, TPC) but had ECOG 0 or 1 recorded within 6 days of randomization.

[c]Defined as relapse while on the first 2 years of adjuvant endocrine therapy or progressive disease within the first 6 months of first-line ET for metastatic breast cancer.

[d]Patients with clinically active CNS metastases (untreated, or symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms) were excluded.

[e]Includes both monotherapy and combination therapy.

[f]Other targeted therapies in the T-DXd and TPC ITT groups included mTOR inhibitors (23.9% and 23.7%), PI3K inhibitors (5.5% and 2.8%), or PARP inhibitors (0.7% and 1.2%).

overall treatment tolerability using the Patient Global Impression-Treatment Tolerability (PGI-TT) scale, and symptomatic AEs using the PRO version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). The EORTC QLQ-C30, EORTC QLQ-BR45, and EQ-5D-5L were completed as follows: before infusion on cycle 1, day 1 (baseline), and every 3 weeks thereafter at day 1 (±3 days) of each cycle until progression on first subsequent therapy (PFS2); at the end-of-treatment visit; and at the progression visit if a patient discontinued treatment for reasons other than progressive disease (PD). PRO-CTCAE items and the PGI-TT were evaluated as above, except that assessments were stopped at the end of treatment rather than continued to PFS2. Additional details on the PRO endpoints are provided in the Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2025.105082.

Statistical analysis

The PRO endpoints were the evaluation of change from baseline (CFB) in EORTC QLQ-C30 and EORTC QLQ-BR45

scale scores and time to deterioration (TTD) in EORTC QLQ-C30 scale scores. All PROs were evaluated in the HER2-low and ITT (HER2-low + HER2-ultralow) populations. Scoring ranged from 0 to 100; a higher score represented a better GHS/QOL or functioning level on the GHS/QOL and functional scales, respectively, and a worse level of symptoms on a symptom scale. A clinically meaningful change was defined as a change (increase or decrease) in the score from a baseline of $\geq$10 points for scales/items from the EORTC QLQ-C30 and EORTC QLQ-BR45 scales.[14,15]

The CFB analysis was carried out using a mixed model for repeated measures, with treatment, visit, treatment-by-visit interaction, and stratification factors as fixed effects, baseline score as a covariate, and the baseline-by-visit interaction. Data cut-off was the date of first recorded on-study PD or 31 weeks after randomization, whichever was earlier; this was based on the expected median PFS in the control group to ensure a similar length of follow-up for both treatments without disease progression.

For each EORTC QLQ-C30 scale, TTD was defined as the time from randomization to the date of the first clinically meaningful deterioration that was confirmed at the next available assessment, at least 14 days apart, regardless of whether the patient withdrew from study treatment or received another anticancer therapy before deterioration (i.e. date of the first deterioration event or censoring minus date of randomization +1). Patients with a single deterioration and no further assessments were treated as deteriorated in the analysis. A log-rank test was used to compare TTD in EORTC QLQ-C30 scores between treatment groups. A *post hoc* TTD analysis evaluating T-DXd versus paclitaxel, nab-paclitaxel, and capecitabine individually was also carried out (for the EORTC QLQ-C30 only).

As exploratory endpoints, the EQ-5D-5L and PGI-TT were reported descriptively and the PRO-CTCAE was represented graphically. Given that PRO endpoints were not part of the multiple testing procedure for DESTINY-Breast06, reported *P*-values are nominal and not adjusted for multiplicity. Additional details on statistical methods are provided in Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2025.105082.

RESULTS

Patient characteristics and treatment

Patients in DESTINY-Breast06 were recruited from 273 sites in 28 countries. From July 2020 to April 2023, 866 patients comprising the ITT population were enrolled and randomized to T-DXd ($n = 436$) or TPC ($n = 430$; 59.8% capecitabine, 24.4% nab-paclitaxel, and 15.8% paclitaxel). Of these patients, 713 comprised the HER2-low population, and 153 comprised the HER2-ultralow population. Patient demographics and baseline clinical characteristics were similar between treatment groups and across populations (Table 1).[11] Patients received a median of 2 previous lines (range 1-5) of endocrine-based therapy for metastatic disease. At the primary data cut-off (18 March 2024), 89 (20.5%) patients in the T-DXd group and 30 (7.2%) in the TPC group remained on treatment. The median duration of treatment was 11.0 months (range 0.4-39.6 months) in the T-DXd group and 5.6 months (0.1-35.9 months) in the TPC group.

PROs

Compliance. In the ITT population, baseline patient compliance for the EORTC QLQ-C30 was higher in the TPC group (74.4%) compared with the T-DXd group (66.5%). For the EORTC QLQ-BR45 also, the baseline compliance rate was higher in the TPC group (73.3%, versus 63.5% in the T-DXd group); however, patient compliance over time was always higher in the T-DXd group, with >70.0% compliance for T-DXd and >53.2% for TPC until week 31 across both questionnaires. The overall compliance rate, which was calculated using data collected at baseline and over time, was similar to T-DXd and TPC for the EORTC QLQ-C30 (65.8% and 69.8%, respectively) and EORTC QLQ-BR45 (62.4% and 67.9%, respectively). Data were consistent in the HER2-low population.

EORTC QLQ-C30 CFB. Baseline scores for all EORTC QLQ-C30 scales were similar between treatment groups in the ITT population (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105082). There was no treatment difference in mean GHS/QOL scores over the analyzed period, that is, until PD or 31 weeks after randomization [adjusted mean difference 1.1 (95% CI −1.2 to 3.4); nominal $P = 0.3506$] (Figure 1; Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105082). There was also no difference between T-DXd and TPC in average scores for physical functioning [adjusted mean difference 0.9 (95% CI −1.2 to 3.0); nominal $P = 0.4102$], role functioning [2.3 (95% CI −0.9 to −5.5); nominal $P = 0.1517$], or any other functioning subscales (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105082). In symptom scales, T-DXd was associated with lower average scores over time for pain compared with TPC [adjusted mean difference −7.2 (95% CI −9.9 to −4.5); nominal $P < 0.0001$], with a clinically meaningful improvement at weeks 25 and 28 (Figure 2A; Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105082). A clinically meaningful deterioration in nausea/vomiting symptoms was seen with T-DXd in the first 3 months (up to week 13; Figure 2B; Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105082). Similarly, a clinically meaningful worsening of appetite loss was observed on weeks 10 and 13 in the T-DXd group. T-DXd was associated with higher average scores for nausea/vomiting [adjusted mean difference 7.2 (95% CI 5.3-9.2); nominal $P < 0.0001$], appetite loss [6.8 (95% CI 3.6-10.0); nominal $P < 0.0001$], and constipation [5.5 (95% CI 2.6-8.4); nominal $P < 0.0002$] symptoms when compared with TPC (Figure 2B; Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105082). Scores for other symptom scales/items (fatigue, dyspnea, insomnia, and diarrhea) were similar across treatment groups (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105082). Results were consistent in the

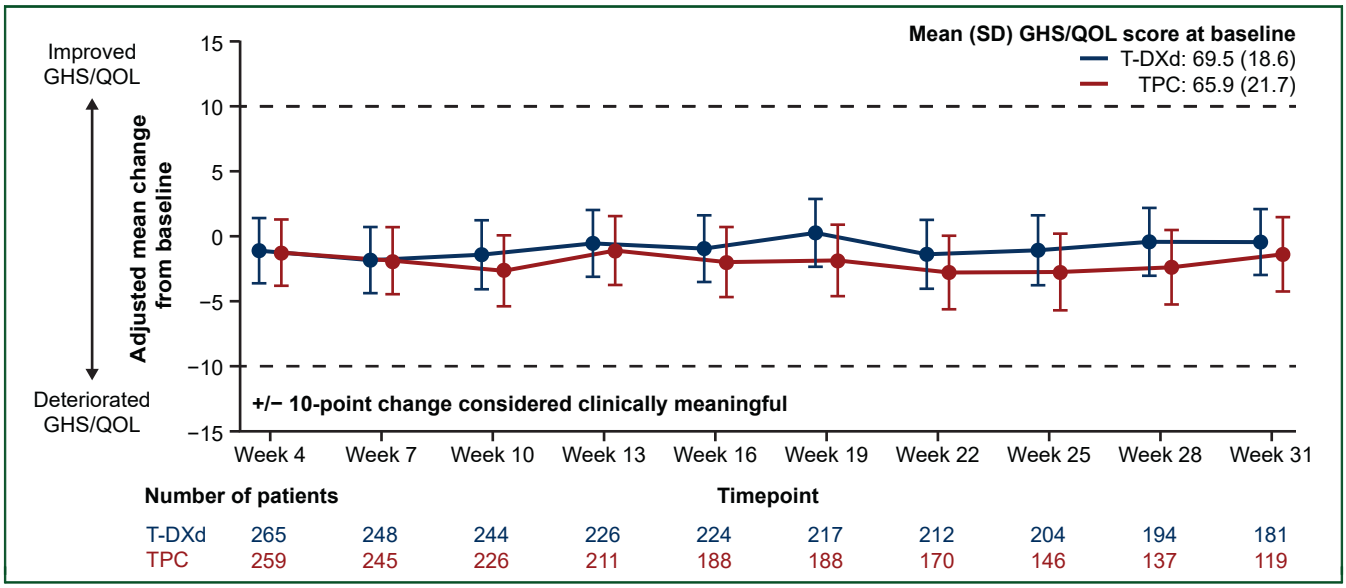


Figure 1. GHS/QOL change from baseline with T-DXd and TPC over time for the ITT population. Bars represent 95% confidence intervals. The baseline is defined as the last assessment on or before randomization, or before the first dose if the assessment is only available after randomization. The analysis was carried out using an MMRM with treatment, visit, treatment-by-visit interaction, prior CDK4/6i use (yes versus no), HER2 IHC expression (IHC 0 with membrane staining versus IHC 1+ versus IHC 2+/ISH−), and prior taxane use in the nonmetastatic setting (yes versus no) as fixed effects, baseline score as a covariate, and the baseline-by-visit interaction. An unstructured covariance matrix was assumed, and the Kenward−Roger approximation was used to estimate the degrees of freedom.
CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; GHS/QOL, global health status/quality of life; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH−, *in situ* hybridization-negative; ITT, intent-to-treat; MMRM, mixed model for repeated measures; SD, standard deviation; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice.

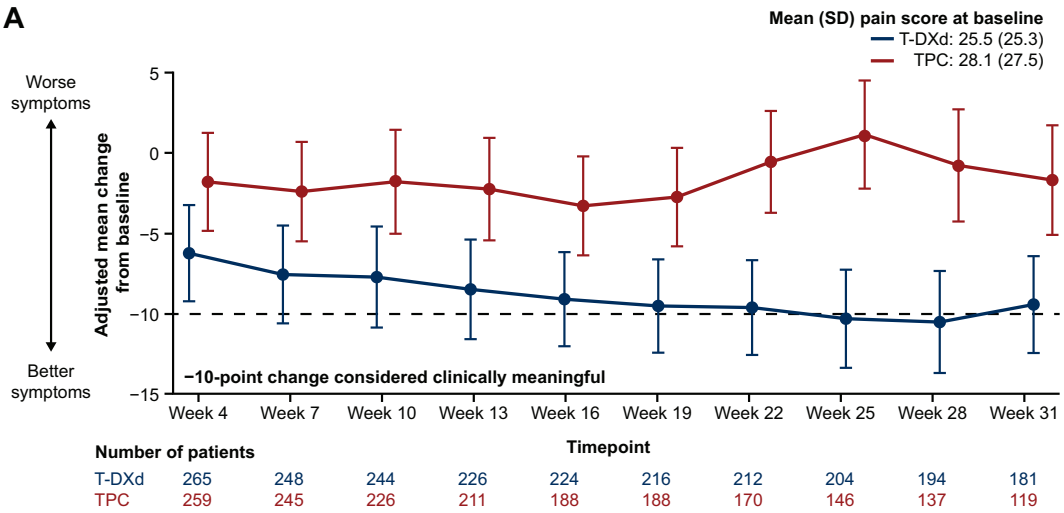
HER2-low population (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.105082).

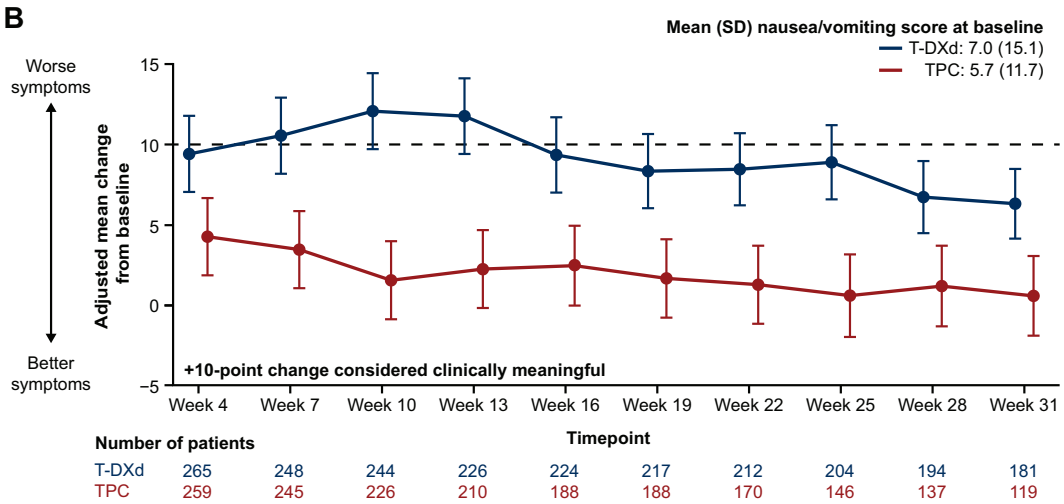
EORTC QLQ-BR45 CFB. Baseline scores for EORTC QLQ-BR45 scales were comparable between treatment groups (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105082). Patients in the TPC group had a clinically meaningful deterioration in skin/mucosal symptoms ('skin mucosis' per the scale) from week 7 onward, while deterioration was low and stable across the 31-week period in the T-DXd group [adjusted mean difference −9.5 (95% CI −11.5 to −7.5); nominal $P < 0.0001$] (Figure 2C; Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105082). To a lesser extent, average scores over time for breast, arm, and ET symptoms also favored T-DXd, while scores for endocrine sexual symptoms favored TPC (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105082). Scores for other functioning and symptom scales were not different between treatments (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105082). Data were consistent in the HER2-low population (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.105082).

EORTC QLQ-C30 TTD. TTD in the GHS/QOL was similar among patients who received T-DXd [median 11.3 months (95% CI 8.3-14.7 months)] versus TPC [10.5 months (95% CI 7.7-13.3 months); hazard ratio 0.93 (95% CI 0.73-1.17); nominal $P = 0.5381$] (Figure 3).

Patients had a longer median TTD and a reduced risk of clinically meaningful deterioration with T-DXd compared with TPC for several EORTC QLQ-C30 functioning subscales (Figures 3 and 4A). For physical functioning, the median TTD was 18.0 months [95% CI 15.9 to not estimable (NE)] with T-DXd and 9.9 months (95% CI 6.9-15.2 months) with TPC; T-DXd reduced the risk of clinically meaningful deterioration by 29% [hazard ratio 0.71 (95% CI 0.55-0.91); nominal $P = 0.0062$] (Figure 4A). The median TTD for role functioning was also longer for T-DXd [10.3 months (95% CI 6.9-14.6 months)] versus TPC [5.5 months (95% CI 4.1-6.9 months)], with a 27% reduced risk of clinically meaningful deterioration [hazard ratio 0.73 (95% CI 0.59-0.91); nominal $P = 0.0057$] (Figure 3). T-DXd also prolonged median TTD versus TPC in emotional functioning (28.2 versus 17.3 months, respectively), with a 26% reduced risk of clinically meaningful deterioration [hazard ratio 0.74 (95% CI 0.56-0.98); nominal $P = 0.0363$] (Figure 3).

TTD was also evaluated in symptom scales (Figures 3 and 4B-D). The median TTD was longer with T-DXd versus TPC for pain: 22.0 (95% CI 17.2 months-NE) versus 6.3 months (95% CI 4.8-9.6 months), respectively (Figure 4B). The risk of clinically meaningful deterioration in pain was reduced by 49% with T-DXd [hazard ratio 0.51 (95% CI 0.39-0.65); nominal $P < 0.0001$]. The median TTD was also longer with T-DXd versus TPC for fatigue [4.3 months (95% CI 3.4-7.7 months) versus 2.9 months (95% CI 2.2-4.2 months), respectively], with a 23% reduced risk of clinically meaningful deterioration [hazard ratio 0.77 (95% CI 0.63-0.95); nominal $P = 0.0127$] (Figure 4C). Conversely, T-DXd increased the risk of clinically meaningful deterioration in gastrointestinal symptoms versus TPC, with a 64% increased risk of clinically meaningful deterioration in nausea/vomiting [hazard ratio 1.64 (95%





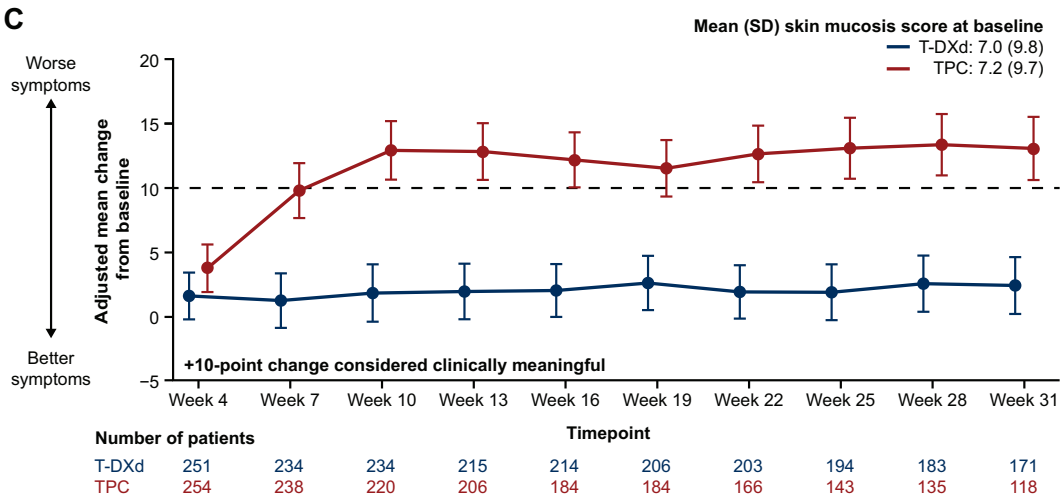


Figure 2. Change from baseline in (A) pain, (B) nausea/vomiting, and (C) skin mucosis symptoms with T-DXd and TPC over time for the ITT population. Bars represent 95% confidence intervals. Baseline is defined as the last assessment on or before randomization, or before the first dose if the assessment is only available after randomization. The analysis was carried out using an MMRM with treatment, visit, treatment-by-visit interaction, prior CDK4/6i use (yes versus no), HER2 IHC expression (IHC 0 with membrane staining versus IHC 1+ versus IHC 2+/ISH−), and prior taxane use in the nonmetastatic setting (yes versus no) as fixed effects, baseline score as a covariate, and the baseline-by-visit interaction. An unstructured covariance matrix was assumed, and the Kenward−Roger approximation was used to estimate the degrees of freedom.
CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH−, *in situ* hybridization-negative; ITT, intent-to-treat; MMRM, mixed model for repeated measures; SD, standard deviation; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice.

Subscale	Number of events		Median TTD, months (95% CI)		Hazard ratio (95% CI)	Nominal *P*-value
	T-DXd	TPC	T-DXd	TPC		
GHS/QOL	142/436	137/430	11.3 (8.3-14.7)	10.5 (7.7-13.3)	0.93 (0.73-1.17)	0.5381
Physical functioning	116/436	137/430	18.0 (15.9-NE)	9.9 (6.9-15.2)	0.71 (0.55-0.91)	0.0062
Role functioning	152/436	174/430	10.3 (6.9-14.6)	5.5 (4.1-6.9)	0.73 (0.59-0.91)	0.0057
Emotional functioning	91/436	104/430	28.2 (18.6-NE)	17.3 (12.4-NE)	0.74 (0.56-0.98)	0.0363
Cognitive functioning	145/436	143/430	11.8 (8.3-16.6)	9.9 (7.8-13.8)	0.88 (0.70-1.11)	0.2955
Social functioning	142/436	149/430	11.7 (7.6-16.3)	7.7 (6.2-10.4)	0.84 (0.67-1.06)	0.1355
Pain	105/436	157/430	22.0 (17.2-NE)	6.3 (4.8-9.6)	0.51 (0.39-0.65)	<0.0001
Fatigue	175/436	201/430	4.3 (3.4-7.7)	2.9 (2.2-4.2)	0.77 (0.63-0.95)	0.0127
Insomnia	96/436	108/430	NE (17.3-NE)	15.2 (12.4-NE)	0.76 (0.58-1.00)	0.0534
Dyspnea	98/436	107/430	20.0 (19.3-NE)	20.8 (13.1-NE)	0.77 (0.58-1.01)	0.0603
Diarrhea	101/436	101/430	29.0 (17.2-NE)	16.5 (13.9-23.4)	0.86 (0.65-1.14)	0.2934
Nausea/ vomiting	178/436	132/430	3.5 (2.8-5.6)	13.8 (7.7-21.5)	1.64 (1.31-2.05)	<0.0001
Appetite loss	152/436	125/430	8.3 (5.0-11.7)	13.8 (9.6-16.1)	1.35 (1.06-1.71)	0.0147
Constipation	147/436	96/430	9.2 (5.5-12.5)	22.0 (15.9-NE)	1.76 (1.36-2.28)	<0.0001

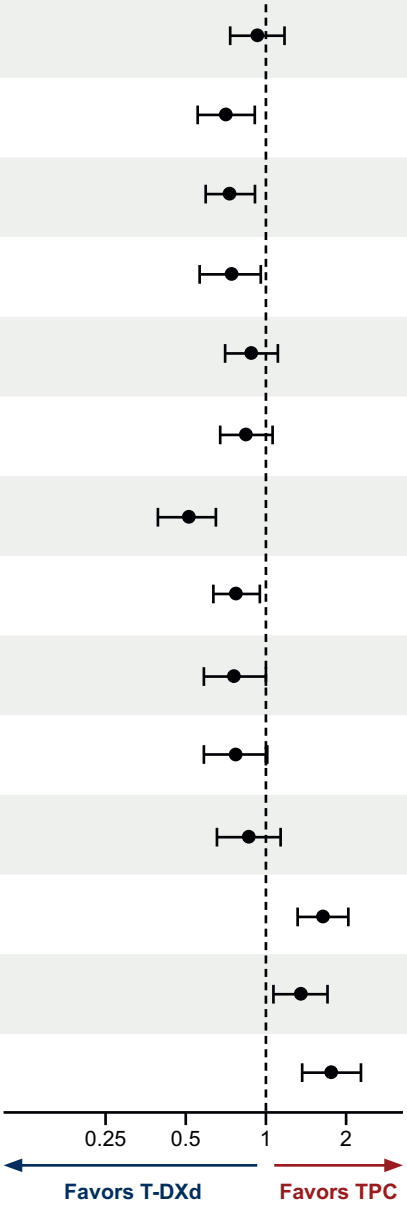


Figure 3. Forest plot of time to deterioration in EORTC QLQ-C30 scales with T-DXd and TPC for the ITT population.
CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; GHS/QOL, global health status/quality of life; ITT, intent-to-treat; NE, not estimable; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice; TTD, time to deterioration.

CI 1.31-2.05); nominal $P < 0.0001$], a 76% increased risk of clinically meaningful deterioration in constipation [hazard ratio 1.76 (95% CI 1.36-2.28); nominal $P < 0.0001$], and a 35% increased risk of clinically meaningful deterioration in appetite loss [hazard ratio 1.35 (95% CI 1.06-1.71); nominal $P = 0.0147$] (Figures 3 and 4D). Data were consistent in the HER2-low population (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105082).

A *post hoc* analysis of TTD in EORTC QLQ-C30 scales was carried out for T-DXd versus paclitaxel, nab-paclitaxel, and capecitabine individually (Supplementary Figure S2A-C, available at https://doi.org/10.1016/j.esmoop.2025.105082). Outcomes for each chemotherapy were broadly consistent with the overall TPC group. Compared with paclitaxel, T-DXd reduced the risk of clinically meaningful deterioration in physical functioning [hazard ratio 0.37 (95% CI 0.19-0.70)] and social functioning [hazard ratio 0.54 (95% CI 0.29-0.99)]

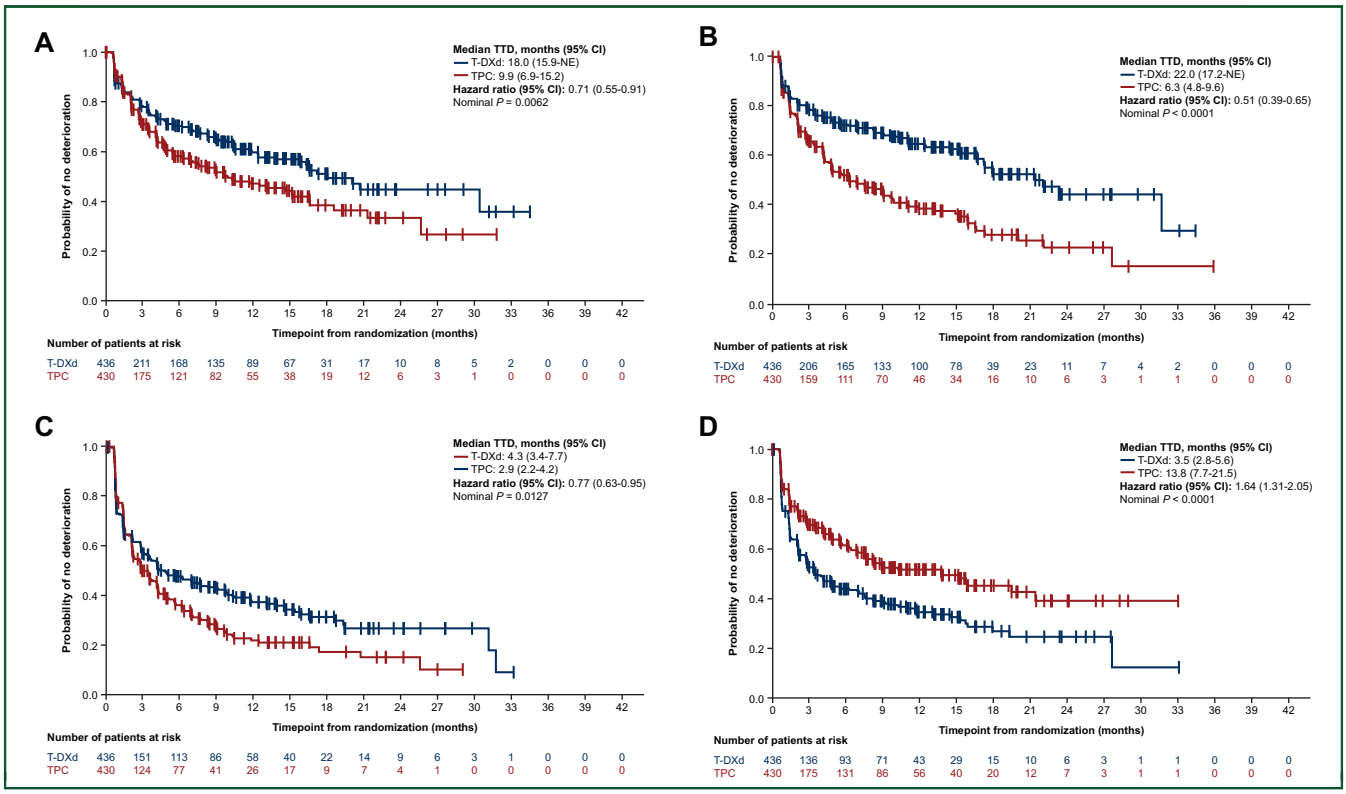


Figure 4. Kaplan–Meier analysis of time to deterioration in (A) physical functioning, (B) pain, (C) fatigue, and (D) nausea/vomiting with T-DXd and TPC for the ITT population. The line indicates a censored observation.
CI, confidence interval; ITT, intent-to-treat; NE, not estimable; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice; TTD, time to deterioration.

(Supplementary Figure S2A, available at https://doi.org/10.1016/j.esmoop.2025.105082), whereas the risk of clinically meaningful deterioration in these functioning scales was similar between T-DXd and capecitabine (Supplementary Figure S2C, available at https://doi.org/10.1016/j.esmoop.2025.105082). For role functioning, there was a 33% reduction in the risk of clinically meaningful deterioration with T-DXd versus capecitabine (hazard ratio 0.67, 95% CI 0.50-0.88; Supplementary Figure S2C, available at https://doi.org/10.1016/j.esmoop.2025.105082). In symptom scales, the risk of clinically meaningful deterioration in pain was reduced with T-DXd versus paclitaxel (hazard ratio 0.34, 95% CI 0.16, 0.67) and capecitabine (hazard ratio 0.48, 95% CI 0.35-0.66; Supplementary Figure S2A and C, available at https://doi.org/10.1016/j.esmoop.2025.105082); similarly, T-DXd reduced the risk of clinically meaningful deterioration in fatigue compared with paclitaxel (hazard ratio 0.57, 95% CI 0.33-0.97) and capecitabine (hazard ratio 0.75, 95% CI 0.57-0.98; Supplementary Figure S2A and C, available at https://doi.org/10.1016/j.esmoop.2025.105082). For nausea/vomiting, the risk of clinically meaningful deterioration was increased for T-DXd compared with paclitaxel (hazard ratio 2.07, 95% CI 1.11-4.06), nab-paclitaxel (hazard ratio 1.62, 95% CI 1.02-2.58), and capecitabine (hazard ratio 1.56, 95% CI 1.18-2.08; Supplementary Figure S2A-C, available at https://doi.org/10.1016/j.esmoop.2025.105082). An increased risk of clinically meaningful deterioration in constipation was observed with T-DXd versus nab-paclitaxel (hazard ratio 1.96, 95% CI 1.18-3.30) and capecitabine [hazard ratio 1.75, 95% CI 1.26-2.46), and an increased risk of clinically meaningful deterioration in appetite loss was observed with T-DXd versus nab-paclitaxel (hazard ratio 1.77, 95% CI 1.12-2.82) (Supplementary Figure S2B and C, available at https://doi.org/10.1016/j.esmoop.2025.105082).

Exploratory PRO endpoints. In the EQ-5D-5L exploratory analysis, mean [standard deviation (SD)] scores for the EQ-5D health state index were consistent across treatment groups at baseline and remained stable over time until week 31 [mean CFB (SD), 0.04 (0.20) versus −0.03 (0.19), respectively; Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.105082). There were no treatment differences in baseline EQ-visual analog scale scores, and mean CFB (SD) scores were similar at week 31 [T-DXd, 1.1 (17.6); TPC, −2.0 (19.9); Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.105082].

When evaluating the maximum (worst) frequency of symptomatic AEs on the PRO-CTCAE, a higher proportion of patients in the T-DXd group versus the TPC group reported nausea (83.6% versus 67.2%), vomiting (47.7% versus 34.7%), and nosebleeds (44.9% versus 33.9%), with more patients in the T-DXd group reporting these symptoms as occurring 'frequently' or 'almost constantly' (Supplementary Figure S3A, available at https://doi.org/10.1016/j.esmoop.2025.105082). When evaluating the worst severity of these symptoms, a higher proportion of patients in the T-DXd group versus the TPC group reported nausea (95.8% versus 88.9%), vomiting (92.7% versus 88.1%), and

nosebleeds (89.1% versus 80.8%), with more patients reporting these symptoms as 'severe' or 'very severe' with T-DXd (Supplementary Figure S3B, available at https://doi.org/10.1016/j.esmoop.2025.105082). Conversely, more patients in the TPC group reported a worse severity of itchy skin symptoms (Supplementary Figure S3B, available at https://doi.org/10.1016/j.esmoop.2025.105082). There were no treatment differences in fatigue and cough severity, or incidence of rash (Supplementary Figure S3B and C, available at https://doi.org/10.1016/j.esmoop.2025.105082).

In the PGI-TT analysis, patients rated T-DXd and TPC as similarly tolerable (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2025.105082). The proportion of patients who were 'not at all bothered by side-effects of cancer treatment' was slightly higher in the T-DXd group compared with the TPC group at baseline (72.4% versus 64.5%, respectively) and at week 31 (30.4% versus 24.8%, respectively).

DISCUSSION

In this PRO analysis of DESTINY-Breast06, no differences were observed between T-DXd and TPC in CFB scores of the EORTC QLQ-C30 GHS/QOL and functioning scales and the EQ-5D-5L over the first 7 months. The risk of clinically meaningful deterioration in GHS/QOL was similar between treatments, and patients considered T-DXd and TPC to be similarly tolerable per the PGI-TT. When considered alongside the positive efficacy data, and the almost twice-longer median treatment duration with T-DXd (11.0 months, versus 5.6 months with TPC), these results indicate that T-DXd provides an efficacy benefit over a prolonged period without detriment to overall HRQOL.

Patients receiving T-DXd had more favorable outcomes across several scales/items of the EORTC QLQ-C30 and EORTC QLQ-BR45: a longer TTD in physical/role/emotional functioning, pain, and fatigue and a lower incidence of skin/mucosal symptoms versus the TPC group. Preservation of functioning has been shown to be important for avoiding dose reductions and treatment discontinuation.[16] Regarding pain symptoms, T-DXd was associated with lower mean CFB scores over time and a 49% reduction in the risk of clinically meaningful deterioration. Effective pain management is a focus of treatment decisions, and a favorable outcome is particularly important given the association with disease burden and poor QOL.[17] The efficacy benefit of T-DXd indicates that an improvement in pain symptoms may be facilitated through an overall reduction in disease burden.[11] Although short overall, the median TTD for fatigue was longer with T-DXd versus TPC, and there were no treatment differences in CFB scores or PRO-CTCAE data. This contrasts with the AE profiles from investigators, with a higher incidence of fatigue reported in the T-DXd group (46.8%) versus TPC (34.3%).[11] Such discrepancies between PRO and investigator-reported outcomes highlight the importance of PRO data in helping to contextualize and interpret safety results.[1,18] A clinically meaningful worsening of skin/mucosal symptoms was observed with TPC but not with T-DXd. Given the high proportion of patients receiving capecitabine in the TPC group (59.8%), this is likely attributable to a common side-effect, palmar-plantar erythrodysesthesia syndrome[19]; indeed, one-third of patients in the TPC group were affected by this AE (32.4%, versus 0.5% with T-DXd). In a *post hoc* TTD analysis of T-DXd versus capecitabine, outcomes in the EORTC QLC-C30 scales for capecitabine were broadly consistent with that of the TPC group as a whole, with a comparably shorter TTD in role functioning, pain, and fatigue versus T-DXd; notably, the TTD in social functioning was similar between T-DXd and capecitabine. Taken together, these data from the EORTC QLQ-C30 and EORTC QLQ-BR45 suggest that key aspects of a patient's QOL are improved or at least maintained with T-DXd treatment compared with TPC.

Patients in the T-DXd group experienced a clinically meaningful increase in nausea/vomiting symptoms during the first 3 months, though CFB scores subsequently decreased and remained stable over time. Patient reports were consistent with that of investigators, with nausea (65.9%) and vomiting (27.2%) among the most common drug-related AEs for T-DXd, although these were primarily low in grade, with only 1.6% and 1.4% of patients reporting grade $\geq$3 nausea and vomiting, respectively.[11] Furthermore, none of the patients discontinued T-DXd treatment because of drug-related nausea and vomiting. Elevated gastrointestinal symptoms among patients receiving T-DXd therefore did not appear to impact the overall preservation of HRQOL. The emetic effects of T-DXd have been documented previously in a similar patient population in DESTINY-Breast04; in that study, T-DXd was associated with a higher risk of deterioration in nausea/vomiting versus TPC.[8] In the current study, this also extended to appetite loss and constipation. As more patients in DESTINY-Breast06 were assigned to capecitabine than in DESTINY-Breast04 (59.8% versus 20.1%, respectively),[5,11] this may have contributed to the different gastrointestinal profiles across the studies. It is also possible that the higher risk of deterioration in constipation and appetite loss was attributable to the antiemetic prophylaxis recommended for patients undergoing T-DXd treatment; however, further investigation of the impact of antiemetic regimens on associated gastrointestinal AEs is warranted. Premedication with a combination of two or three antiemetics [e.g. dexamethasone with a 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonist and/or a neurokinin-1 receptor antagonist, and other medicinal products as indicated] was recommended before T-DXd infusions; however, this was prescribed at the investigator's discretion and not mandated. Overall, 74.1% of patients in the T-DXd group received antiemetic prophylaxis with at least one agent at any time during treatment (with 57.6% receiving at least one antiemetic agent before cycle 1), indicating there is still a need to increase optimal antiemetic use. Recent data suggest that a triple regimen of olanzapine, a 5-HT_3 receptor antagonist, and dexamethasone is effective in preventing delayed and persistent nausea and vomiting in T-DXd-treated patients.[20] Educating clinicians on the importance of preventing and identifying early gastrointestinal symptoms

should be a key area of focus to better support patients undergoing T-DXd treatment.

The PRO findings presented here add to a substantial body of evidence for the preservation of HRQOL with T-DXd in mBC. DESTINY-Breast02, -Breast03, and -Breast04 demonstrated GHS/QOL maintenance for the duration of T-DXd treatment, and the TTD for most prespecified PRO measures (including functioning, pain, and arm symptoms) favored T-DXd versus comparators, consistent with the findings of DESTINY-Breast06.[8,10,21,22] Collectively, T-DXd has demonstrated favorable HRQOL outcomes versus several comparators, including capecitabine and trastuzumab emtansine.[10,21]

The overall patient compliance for questionnaire completion was lower than that of previous DESTINY-Breast studies[8,21,22]; however, there was a 100% evaluability rate in the questionnaires received. While baseline compliance was lower for T-DXd than TPC, rates improved thereafter and were always higher in the T-DXd group, ranging from 70% to 88% during weeks 4-31 for both EORTC questionnaires. In addition, there was no treatment difference in dyspnea, despite interstitial lung disease (ILD)/pneumonitis being an important AE of special interest (AESI) for T-DXd. This suggests that patient-reported dyspnea has limited relevance to clinical ILD/pneumonitis (indeed, oxygen saturation is considered a more useful indicator) and that future T-DXd trials could benefit from including alternative PRO measures to provide better insights into AESIs; however, aligning PROs with clinical findings is challenging, and interpretation is limited by low rates of AESIs and the impact of clinical confounders (e.g. fatigue and anemia) on ILD/pneumonitis. While alopecia is a common AE associated with T-DXd treatment,[5,11] robust interpretation of the EORTC QLQ-BR45 'upset by hair loss' scale was not possible owing to a high number of patients being excluded from the analysis because they did not have hair loss at the times of assessment, as outlined in the scoring manual.[15] Finally, the open-label trial design may be considered a limitation owing to potential bias in patient responses, although recent studies have indicated that patients' perspectives on HRQOL are not impacted by the knowledge of their assigned treatment.[23-26]

In conclusion, T-DXd maintained GHS/QOL while delaying deterioration in physical/role/emotional functioning, pain, and fatigue versus TPC, albeit with more gastrointestinal symptoms. These PRO data complement the clinical efficacy and safety of T-DXd and further support T-DXd as a new therapeutic option after one or more lines of endocrine-based therapy in patients with HR+, HER2-low, or HER2-ultralow mBC.

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DATA SHARING

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at https://www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca's Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

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